CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074958

Trade Name : CLOMIPRAMINE HCL CAPSULES

Generic Name: Clomipramine HCL Capsules 25mg, 50mg and 75mg

Sponsor : Lemmon Company

Approval Date: August 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074958

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074958

APPROVAL LETTER

ANDA 74-958

AUG 26 1997

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Madam:

This is in reference to your abbreviated new drug application dated September 9, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, and 75 mg.

Reference is also made to your amendments dated March 4, March 7, July 25, and July 31, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, and 75 mg are bioequivalent and, therefore therapeutically equivalent, to the listed drug (Anafranil® Capsules 25 mg, 50 mg, and 75 mg, respectively, of Novartis Pharmaceutical Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074958

FINAL PRINTED LABELING

NDC 0093-0960-01 2 6 1997

CLOMIPRAMINE HYDROCHLORIDE Capsules 75 mg

Each capsule contains:
Clomipramine Hydrochloride 75 mg

Caution: Federal law prohibits dispensing without prescription.

100 CAPSULES

LEMMON

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight container as defined in the USP, with a child-resistant closure (as required).

Protect from moisture.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 2/97

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
LEMMON COMPANY
Sellersville, PA 18960

N 3 0093-0960-01 7

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight container as defined in the USP, with a child-resistant closure (as required).

Protect from moisture.

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Jerusalem, 91010, Israel
Manufactured For:
LEMMON COMPANY
Sellersville, PA 18960

N 3 0093-0960-10 9

LEMMON

1000 CAPSULES

Each capsule contains:
Clomipramine Hydrochloride 75 mg

Caution: Federal law prohibits dispensing without prescription.

NDC 0093-0960-10

CLOMIPRAMINE HYDROCHLORIDE Capsules 75 mg

6 9 6 1997

NDC 0093-0958-10

CLOMIPRAMINE HYDROCHLORIDE Capsules 50 mg

JUL 26 1997

Each capsule contains:
Clomipramine Hydrochloride 50 mg

Caution: Federal law prohibits dispensing without prescription.

1000 CAPSULES

LEMMON

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight container as defined in the USP, with a child-resistant closure (as required).

Protect from moisture.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Jerusalem, 91010, Israel

Manufactured For:
LEMMON COMPANY
Sellersville, PA 18960

N 3 0093-0958-10 6

NDC 0093-0958-01

CLOMIPRAMINE HYDROCHLORIDE Capsules 50 mg

JUL 26 1997

Each capsule contains:
Clomipramine Hydrochloride 50 mg

Caution: Federal law prohibits dispensing without prescription.

100 CAPSULES

LEMMON

Usual Dosage: See package insert for full prescribing information.

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Manufactured For:
LEMMON COMPANY
Sellersville, PA 18960

N 3 0093-0958-01 4

NDC 0093-0956-10 2 6 1997

CLOMIPRAMINE HYDROCHLORIDE Capsules 25 mg

Each capsule contains:
Clomipramine Hydrochloride 25 mg

Caution: Federal law prohibits dispensing without prescription.

100 CAPSULES

LEMMON

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°- 30°C (59°- 86°F).

Dispense contents in a tight container as defined in the USP, with a child-resistant closure (as required).

Protect from moisture.

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Jerusalem, 91010, Israel

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LEMMON COMPANY
Sellersville, PA 18960

N 0093-0956-10 2

NDC 0093-0956-01 1997

CLOMIPRAMINE HYDROCHLORIDE Capsules 25 mg

Each capsule contains:
Clomipramine Hydrochloride 25 mg

Caution: Federal law prohibits dispensing without prescription.

100 CAPSULES

LEMMON

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15°- 30°C (59°- 86°F).

Dispense contents in a tight container as defined in the USP with a child-resistant closure (as required).

Protect from moisture.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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N 0093-0956-01 0

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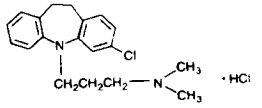
CLOMIPRAMINE HYDROCHLORIDE CAPSULES

0956
0958
0960 Rev. A 2/97

DESCRIPTION

Clomipramine hydrochloride is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



$C_{19}H_{23}ClN_2 \cdot HCl$ M.W. 351.3

Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane.

Each capsule, for oral administration, contains 25 mg, 50 mg, or 75 mg of clomipramine hydrochloride. In addition, each capsule contains the following inactive ingredients: pregelatinized starch, colloidal silicon dioxide, magnesium stearate, titanium dioxide, shellac, black iron oxide, and gelatin. Each 25 mg capsule contains D&C Red No. 28, FD&C Red No. 40, D&C Yellow No. 10, FD&C Blue No. 1. Each 50 mg capsule contains FD&C Blue No. 1. Each 75 mg capsule contains red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Pharmacokinetics

Absorption/Bioavailability: Clomipramine from a capsule is as bioavailable as clomipramine from a solution. The bioavailability of clomipramine from capsules is not significantly affected by food.

In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of clomipramine and clomipramine's major active metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day.

The relationship between dose and clomipramine/desmethylclomipramine concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of clomipramine occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). After multiple daily doses of 150 mg of clomipramine, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for clomipramine and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for desmethylclomipramine. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: Clomipramine distributes into cerebrospinal fluid (CSF) and brain and into breast milk. Desmethylclomipramine also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of clomipramine is approximately 97%, principally to albumin, and is independent of clomipramine concentration. The interaction between clomipramine and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of clomipramine in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of clomipramine and desmethylclomipramine were only about 0.8-1.3% of the dose administered. Clomipramine does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{ss} and AUC for clomipramine and desmethylclomipramine may increase disproportionately with increasing oral doses suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of clomipramine and desmethylclomipramine are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, clomipramine and desmethylclomipramine may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for clomipramine. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for clomipramine is approximately 2.5 and for desmethylclomipramine is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of clomipramine have not been determined.

Interactions: Coadministration of haloperidol with clomipramine increases plasma concentrations of clomipramine. Coadministration of clomipramine with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated clomipramine better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of clomipramine were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Clomipramine Hydrochloride Capsules are indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of clomipramine for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking clomipramine experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. Clomipramine treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of clomipramine for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Clomipramine Hydrochloride Capsules are contraindicated in patients with a history of hypersensitivity to clomipramine or other tricyclic antidepressants.

Clomipramine should not be given in combination, or within 14 days before or after treatment, with a monoamino oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Clomipramine is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of clomipramine hydrochloride use.

The observed cumulative incidence of seizures among patients exposed to clomipramine hydrochloride at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7%, (25 of 3519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of clomipramine hydrochloride greater than 250 mg is limited, given that the plasma concentration of clomipramine may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Caution should be used in administering clomipramine to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, clomipramine had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between clomipramine treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking clomipramine while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery; driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking clomipramine in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with clomipramine in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with clomipramine have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with clomipramine. As with tricyclic antidepressants to which it is closely related, clomipramine may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of clomipramine in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to clomipramine.

Hepatic Changes: During premarketing testing, clomipramine was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with clomipramine, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with clomipramine use. As is the case with tricyclic antidepressants to which clomipramine is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine was used in combination with other drugs. When clomipramine and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with clomipramine in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving clomipramine, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving clomipramine had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of clomipramine with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since

there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with clomipramine hydrochloride should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, clomipramine should be used with caution in the following:

(1) Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;

(2) Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;

(3) Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;

(4) Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe clomipramine hydrochloride:

(1) The risk of seizure (see WARNINGS);

(2) The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction);

(3) Since clomipramine may impair the mental and/or physical abilities required for the performance of complex tasks, and since clomipramine is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS);

(4) Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since clomipramine may exaggerate their response to these drugs;

(5) Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;

(6) Patients should notify their physician if they are breast-feeding.

Drug Interactions

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Clomipramine should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when clomipramine is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin), and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Interactions).

Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clomipramine by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy. Teratogenic Effects. Pregnancy Category C.

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine until delivery. Clomipramine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clomipramine has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in pediatric patients (10-17 years of age), 46 outpatients received clomipramine for up to 8 weeks. In addition, 150 adolescent patients have received clomipramine in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with clomipramine may have on the growth and development of pediatric patients.

The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine in pediatric patients under the age of 10.

Use in Elderly

Clomipramine has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received clomipramine for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received clomipramine in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received clomipramine in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving clomipramine (N=322) or placebo (N=319) or children treated with clomipramine (N=46) or placebo (N=44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting Event)

	Adults		Children and Adolescents	
Body System/ Adverse Event*	**Clomipramine (N=322)**	**Placebo (N=319)**	**Clomipramine (N=46)**	**Placebo (N=44)**
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7
Libido change	21	3	-	-
Nervousness	18	2	4	2
Myoclonus	13	-	2	-
Increased appetite	11	2	-	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	-
Twitching	7	1	4	5
Impaired concentration	5	2	-	-
Depression	5	1	-	-
Hypertonia	4	1	2	-
Sleep disorder	4	-	9	5
Psychosomatic disorder	3	-	-	-
Yawning	3	-	-	-
Confusion	3	-	2	-
Speech disorder	3	-	-	-
Abnormal dreaming	3	-	-	2
Agitation	3	-	-	-
Migraine	3	-	-	-
Depersonalization	2	-	2	-
Irritability	2	2	2	-
Emotional lability	2	-	-	2
Panic reaction	1	-	2	-
Aggressive reaction	-	-	2	-
Paresis	-	-	-	-
Skin and Appendages				
Increased sweating	29	3	9	-
Rash	8	1	4	2
Pruritus	6	-	2	2
Dermatitis	2	-	-	2
Acne	2	2	-	5
Dry skin	2	-	-	5
Urticaria	1	-	-	-
Abnormal skin odor	-	-	2	-
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	-	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	-
Flatulence	6	3	-	2
Tooth disorder	5	-	-	-
Gastrointestinal disorder	2	-	-	2
Dysphagia	2	-	-	-
Esophagitis	1	-	-	-
Eructation	-	-	2	2
Ulcerative stomatitis	-	-	2	-
Body as a Whole				
Fatigue				

6 1997

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting Event)

Body System/ Adverse Event*	Adults: Clomipramine (N=322)	Adults: Placebo (N=319)	Children and Adolescents: Clomipramine (N=46)	Children and Adolescents: Placebo (N=44)
Body as a Whole (cont.)				
Weight increase	18	1	2	-
Flushing	8	-	7	-
Hot flushes	5	-	2	-
Chest pain	4	4	7	-
Fever	4	-	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	-	-
Chills	2	1	-	-
Weight decrease	-	-	7	-
Otitis media	-	-	4	5
Asthenia	-	-	2	-
Halitosis	-	-	2	-
Cardiovascular System				
Postural hypotension	6	-	4	-
Palpitation	4	2	4	-
Tachycardia	4	-	2	-
Syncope	-	-	2	-
Respiratory System				
Pharyngitis	14	9	-	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	-	7	2
Epistaxis	2	-	-	2
Dyspnea	-	-	2	-
Laryngitis	-	1	2	-
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	-	-
Micturition frequency	5	3	-	-
Urinary retention	2	-	7	-
Dysuria	2	2	-	-
Cystitis	2	-	-	-
Female Patients Only	**(N=182)**	**(N=167)**	**(N=10)**	**(N=21)**
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	-	-	-
Menstrual disorder	4	2	-	-
Vaginitis	2	-	-	-
Leukorrhea	2	-	-	-
Breast enlargement	2	-	-	-
Breast pain	1	-	-	-
Amenorrhea	1	-	-	-
Male Patients Only	**(N=140)**	**(N=152)**	**(N=36)**	**(N=23)**
Ejaculation failure	42	2	6	-
Impotence	20	3	-	-
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	-	4	-
Tinnitus	6	-	4	-
Abnormal lacrimation	3	2	-	-
Mydriasis	2	-	-	-
Conjunctivitis	1	-	-	-
Anisocoria	-	-	2	-
Blepharospasm	-	-	2	-
Ocular allergy	-	-	2	-
Vestibular disorder	-	-	2	2
Musculoskeletal				
Myalgia	13	9	-	-
Back pain	6	6	-	-
Arthralgia	3	5	-	-
Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				
Thirst	2	2	-	2

*Events reported by at least 1% of clomipramine patients are included.

Other Events Observed During the Premarketing Evaluation of Clomipramine
During clinical testing in the U.S., multiple doses of clomipramine were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to clomipramine who experienced an event of the type cited on at least one occasion while receiving clomipramine. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with clomipramine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* - general edema, increased susceptibility to infection, malaise. *Rare* - dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* - abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* - aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* - abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* - cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent*- hypothyroidism. Rare - goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* - lymphadenopathy. *Rare* - leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* - dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* - fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* - arthrosis. *Rare* - dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent* - abnormal thinking, vertigo. *Infrequent* - abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* - anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* - bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* - cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* - alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* - chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* - abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* - blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* - endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* - albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE
Clomipramine has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with clomipramine discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential clomipramine abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received clomipramine hydrochloride for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for clomipramine in foreign marketing, it is not possible to predict the extent to which clomipramine might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE
Human Experience
In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with clomipramine either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine overdose, the lowest dose associated with a fatality was 750 mg. Based upon postmarketing reports in the United Kingdom, clomipramine's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms
Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of clomipramine may not reflect the severity of poisoning: they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment
The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation may be necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

In the alert patient, the stomach should be emptied promptly by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Installation of activated charcoal slurry may help reduce absorption of clomipramine.

External stimulation should be minimized to reduce the tendency for convulsions. If anticonvulsants are necessary, diazepam and phenytoin may be useful. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, and, if necessary, a vasopressor agent by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of clomipramine in tissues.

The slow intravenous administration of physostigmine salicylate has been used as a last resort to reverse severe CNS anticholinergic manifestations of overdosage with tricyclic antidepressants; however, it should not be used routinely, since it may induce seizures and cholinergic crises.

DOSAGE AND ADMINISTRATION
The treatment regimens described below are based on those used in controlled clinical trials of clomipramine in 520 adults, and 91 children and adolescents with OCD. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both clomipramine and its active metabolite, desmethylclomipramine, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)
Treatment with clomipramine hydrochloride should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)
As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)
While there are no systematic studies that answer the question of how long to continue clomipramine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of clomipramine after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED
Clomipramine Hydrochloride Capsules are available as follows:

Clomipramine Hydrochloride Capsules 25 mg: No. 2 capsule with a white body and a medium orange cap, imprinted "93" "956" on both the body and the cap, available in bottles of 100 and 1000.

Clomipramine Hydrochloride Capsules 50 mg: No. 1 capsule with a white body and light blue cap, imprinted "93" "958" on both the body and the cap, available in bottles of 100 and 1000.

Clomipramine Hydrochloride Capsules 75 mg: No. 0 capsule with a white body and carmel cap, imprinted "93" "960" on both the body and the cap, available in bottles of 100 and 1000.

Store at controlled room temperature 15° - 30° C (59° - 86°F).

Protect from moisture.

Dispense contents in a tight container as defined in the USP, with a child-resistant closure (as required).

CAUTION: Federal law prohibits dispensing without prescription.

ANIMAL TOXICOLOGY
Testicular and lung changes commonly associated with tricyclic compounds have been observed with clomipramine. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
LEMMON COMPANY
Sellersville, PA 18960

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074958

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO: 2

2. ANDA # 74-958

3. NAME AND ADDRESS OF APPLICANT

Lemmon Company
650 Cathill RD.
Sellersville, PA 18960

4. LEGAL BASIS FOR SUBMITTED APPLICATION:

The firm certifies that to the best of their knowledge there are no patents which claim the listed drug product Anafranil and there exist no listed exclusivities for the referenced drug product.

7. NONPROPRIETARY NAME

Clomipramine Hydrochloride

9. AMENDMENTS AND OTHER DATES:

Original 9/9/96
Amendment 3/4/97
Amendment 3/7/97
Amendment 7/31/97

10. PHARMACOLOGICAL CATEGORY

Treatment of obsessive and compulsive behaviors

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Capsule

14. POTENCY

25, 50, and 75 mg

15. CHEMICAL NAME AND STRUCTURE

3-(3-chloro-10,11-dihydro-5H-dibena[G,f]azepin-5-yl)propyldimethylamine hydrochloride

17. COMMENTS:

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

8/12/97

Nashed E. Nashed, Ph.D. 8/12/97

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 74-958
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed/8/12/97
HFD-627/P.Schwartz/ 8/12/97
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F/t by: gp/8/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074958

BIOEQUIVALENCE REVIEW(S)

D W

ANDA 74-958

Lemmon Company
Attention: Deborah Jaskot
650 Cathill Road
Sellersville PA 18960

APR 14 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Clomipramine Hydrochloride Capsules 25 mg, 50 mg and 75 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of 0.1 N HCL at 37°C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (Q) of the labeled amount of clomipramine hydrochloride in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

fw Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

9 w

APR - 8 1997

Clomipramine Hydrochloride Capsules	Lemmon
25 mg, 50 mg and 75 mg	Sellersville, PA
ANDA #74-958	Submission Date:
Reviewer: Moo Park	March 7, 1997
Filename: 74958a.397	

Review of an Amendment

I. Objectives

Review of dissolution data submitted in an amendment in response to the deficiency letter dated February 6, 1997.

II. Background

The *in vivo* bioequivalence studies (submission date: 9/9/96; review date: 1/31/97) conducted under fasting and nonfasting conditions by Lemmon on its Clomipramine Capsules, 50 mg strength, lot #K19533, comparing it to Basel's Anafranil® Capsules, 50 mg strength, lot #1T175760, were acceptable. The firm, however, submitted comparative dissolution testing data using non-FDA method. The firm was requested to perform the dissolution testing using FDA method.

III. Comments

1. The firm submitted new dissolution data based on the FDA method (Pharmacopeial Forum method, March-April, 1995). The new comparative dissolution data on 25 mg, 50 mg and 75 mg strengths test products are acceptable as shown in Table 1. The FDA method is shown below:

Medium and Volume	0.1 N HCL; 500 mL
Apparatus and rpm	Paddle; 50 rpm
Tolerances	(Q) in 30 min
Assay Method	

2. Waiver requests for the 25 mg and 75 mg strengths test

products are granted.

IV. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting and nonfasting conditions by Lemmon on its Clomipramine Capsules, 50 mg strength, lot #K19533, comparing it to Basel's Anafranil[R] Capsules, 50 mg strength, lot #1T175760, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Lemmon's Clomipramine Capsules, 50 mg strength, is bioequivalent to Basel's Anafranil[R] Capsules, 50 mg strength.

2. The FDA dissolution testing conducted by Lemmon on its Clomipramine Capsules, 25 mg strength, lot #K19532, 50 mg strength, lot #K19533, and 75 mg strength, lot #K19534, is acceptable. The formulations for the 25 mg and 75 mg strength capsules are proportional to the 50 mg strength capsules of the test product which underwent two acceptable bioequivalence studies (submission date: 9/9/1996). Waivers of *in vivo* bioequivalence study requirements for the 25 mg and 75 mg strength capsules of the test product are granted. The 25 mg and 75 mg strength capsules of the test product are therefore deemed bioequivalent to Basel's Anafranil[R] Capsules, 25 mg and 75 mg strengths capsules.

3. The FDA dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1 N HCL at 37°C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of clomipramine hydrochloride in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view the firm met the *in vivo* bioequivalence and *in vitro* dissolution testing requirements and the studies are acceptable.

The firm should be informed of recommendations.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

Table 1. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Clomipramine Hydrochloride Capsules					
Strength	25 mg, 50 mg and 75 mg					
ANDA Number	ANDA #74-958					
Applicant	Lemmon					
Reference Drug Product	Basel's Anafranil[R] Capsules					
II. USP Method for Dissolution Testing						
Medium and Volume	0.1 N HCL; 500 mL					
Apparatus and rpm	Paddle; 50 rpm					
Time						
Tolerances	(Q) in 30 min					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No: K-19532 Strength: 25 mg No of Units: 12			Reference Product Lot No: 1T175496 Strength: 25 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	93.6		7.7	93.3		4.6
15	96.2		5.7	94.9		4.2
30	97.7		5.7	96.9		3.3

Time	Test Product Lot No: K-19533 Strength: 50 mg No of Units: 12			Reference Product Lot No: 1T175760 Strength: 50 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	94.8		5.9	89.2		3.6
15	97.3		4.6	93.3		4.3
30	98.4		4.5	96.6		3.3

Time	Test Product Lot No: K-19534 Strength: 75 mg No of Units: 12			Reference Product Lot No: 1T167163 Strength: 75 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	91.8		3.6	89.7		5.1
15	94.8		4.0	96.9		3.6
30	96.1		3.1	99.1		2.4

D/V

JAN 3 1 1997

Clomipramine Hydrochloride Capsules	Lemmon
25 mg, 50 mg and 75 mg	Sellersville, PA
ANDA #74-958	Submission Date:
Reviewer: Moo Park	September 9, 1996
Filename: 74958sdw.996	

Review of Two Bioequivalence Studies, Dissolution Data and Two Waiver Requests

I. Objectives

Review of:

- Two-way crossover *in vivo* bioequivalence study comparing Lemmon's Clomipramine Hydrochloride Capsules, 50 mg strength, to Basel's Anafranil^{R} (Clomipramine Hydrochloride) Capsules, 50 mg strength, following administration of a 50 mg dose under fasting conditions.
- Three-way crossover *in vivo* bioequivalence study comparing Lemmon's Clomipramine Hydrochloride Capsules, 50 mg strength, to Basel's Anafranil^{R} (Clomipramine Hydrochloride) Capsules, 50 mg strength, following administration of a 50 mg dose under nonfasting conditions.
- Dissolution data for 25 mg, 50 mg, and 75 mg capsules.
- A waiver request for 25 mg and 75 mg capsules.

II. Background

Clomipramine hydrochloride is an antiobsessional drug that belongs to the class (dibenzazepine) of tricyclic antidepressants. The drug is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD) and is presumed to influence through its effects on serotonergic neuronal transmission by possibly inhibiting the reuptake of serotonin (5-HT). Clomipramine hydrochloride is

freely soluble in water.

Following an oral dose of clomipramine hydrochloride, maximum plasma concentrations occur within 2-6 hours (mean 4.7 hr). The protein binding of the drug is approximately 97%, principally to albumin, and independent of clomipramine hydrochloride concentration. The bioavailability of the drug from capsules is not significantly affected by food. In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{ss}) and AUC of clomipramine and its major metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. This finding suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited. Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on Obsessive-Compulsive Disorder behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. Following a 150-mg dose, the half-life of clomipramine ranges from 19 to 37 hours (mean 32 hr) and that of desmethylclomipramine ranges from 54 to 77 hours (mean 69 hr).

The most commonly observed adverse effects associated with clomipramine were gastrointestinal complaints including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints including changed libido, ejaculatory failure, impotence, a micturition disorder; and other miscellaneous complaints including fatigue, sweating, increased appetite, weight gain and visual changes.

Clomipramine Hydrochloride is available commercially as Anafranil^{R} oral capsule, 25 mg, 50 mg and 75 mg, manufactured by Basel Pharmaceuticals.

III. Study Details

A. Study under fasting conditions

1. Protocol #B-07195; P95-352
2. Applicant: Lemmon, Sellersville, PA
3. Study sites:

Clinical study:

Analytical:

4. Investigators:
   Medical investigator:

   Analytical:

   Statistics:

5. Clinical study dates: Period 1=10/28/95-11/7/95
   Period 2=12/2/95-12/12/95

   Assay dates: 4/30/96-5/18/96

6. Study design: Open-label, randomized, single dose, two-way crossover design.

7. Subjects: Thirty-eight (38) healthy male subjects and no alternates were enrolled. All subjects completed an acceptable medical history, physical examination, clinical laboratory, an electrocardiogram, screens for HIV 1 & 2 antibody, hepatitis B surface antigen and drugs of abuse prior to study initiation.

   Exclusion Criteria:

   a. Volunteers with a recent history of drug or alcohol addiction or abuse.

   b. Volunteers with the presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system (s) or psychiatric disease (as determined by the medical investigator).

   c. Volunteers whose clinical laboratory test values fell outside the accepted reference ranges and were confirmed on repeat testing, if the values were deemed clinically significant.

   d. Volunteers demonstrating a positive hepatitis B surface antigen screen or a reactive HIV 1 & 2 antibody screen.

   e. Volunteers with a history of allergic response (s) to clomipramine hydrochloride or related drugs.

f. Volunteers with a history of clinically significant allergies including drug allergies.

g. Volunteers with any clinically significant illness during the 4 weeks prior to Period I dosing (as determined by the medical investigator).

h. Volunteers who currently used tobacco products.

i. Volunteers who had taken any drug known to induce or inhibit hepatic drug metabolism in the 30 days prior to Period I dosing.

j. Volunteers who reported donating greater than 150 mL of blood within 30 days prior to Period I dosing. All subjects were advised not to donate blood until four weeks after completing the study.

k. Volunteers who reported donating plasma (e.g. plasmapheresis) within 30 days prior to Period I dosing. All subjects were advised not to donate plasma until four weeks after completing the study.

l. Volunteers who reported receiving any investigational drug within 30 days prior to Period I dosing.

m. Volunteers who reported taking any prescription medication in the 14 days prior to Period I dosing.

8. Product information:

1. Test Product: Clomipramine HCl Capsules, 50 mg (Teva Pharmaceutical Industries, Ltd., Provided by LEMMON Company; Lot No. K-19533, Exp. Date: None Shown, Mfg. Date: Feb 22, 1995)

2. Reference Product: Anafranil^{R} Capsules, 50 mg (Basel Pharmaceuticals, Division of Ciba-Geigy Corp.; Lot No. 1TI75760, Exp. Date: Nov '97)

9. Dosing: Subjects received a single, oral dose of a 50 mg capsule with 240 mL of water after an overnight fast.

10. Food and fluid intake:

(1) Fluid Intake: No fluid except that given with drug administration was allowed from 1 hour before dosing until 2

nours after dose administration. At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after the dose, water was allowed ad lib, if requested, but was generally controlled during confinement and limited to approximately 2400 mL from the time of dosing until release from the study site.

(2) Fasting: All subjects fasted from 10 hours prior to dose administration until at least 4 hours after dosing during each study period. However, clear fluids, such as water, were allowed during fasting.

(3) Type of Meals: Subjects were served standardized meals and beverages. Meals were the same in content and quantity during each study period.

(4) Diet Restriction: No caffeine or xanthine-containing food or drink were allowed during the confinement portions of the study.

11. Confinement: From 10 hours before dosing until after the 24-hour blood draw in each period.

12. Washout period: 35 days.

13. Blood samples: Serial blood samples of 10 mL each were collected in Vacutainers with EDTA at the following times: predose (0), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 192, and 240 hours during each study period. The vacutainer samples were then transferred to the processing laboratory and centrifuged at 2400 RPM for 15 minutes at 4°C. The plasma was pipetted immediately with polyethylene pipettes into polypropylene screw-top transport tubes. The plasma samples were immediately placed in the freezer and stored at a temperature of -20°C or colder.

14. IRB and informed consent: The investigators provided the Institutional Review Board (IRB) with all appropriate material, including a copy of the protocol and consent document. The trial was not initiated until appropriate IRB written approval of the research plan and the consent document was obtained by the investigators and copies received by the Sponsor.

15. Pharmacokinetic and statistical analysis: SAS-GLM procedures were used on AUCT, AUCI, CMAX, TMAX, KE, THALF and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for log-

transformed AUCT, AUCI, and CMAX.

B. Study under nonfasting conditions

1. Protocol #B-072055; P95-353
2. Applicant: Lemmon, Sellersville, PA
3. Study sites:
   Clinical study:

   Analytical:

4. Investigators:
   Medical investigator:

   Analytical:

   Statistics:

5. Clinical study dates: Period 1=10/29/95-11/8/95
   Period 2=12/3/95-12/13/95
   Period 3=1/7/96-1/17/96

   Assay dates: 4/22/96-5/2/96

6. Study design: Open-label, randomized, single dose, three-way crossover design.

7. Subjects: Eighteen (18) healthy male subjects and no alternates were enrolled. All subjects completed an acceptable medical history, physical examination, clinical laboratory, an electrocardiogram, screens for HIV 1 & 2 antibody, hepatitis B surface antigen and drugs of abuse prior to study initiation.

8. Product information:

1. Test Product: Clomipramine HCl Capsules, 50 mg (Teva Pharmaceutical Industries, Ltd., Provided by LEMMON Company; Lot No. K-19533, Exp. Date: None Shown, Mfg. Date: Feb 22, 1995)

2. Reference Product: Anafranil^{R} Capsules, 50 mg (Basel Pharmaceuticals, Division of Ciba-Geigy Corp.; Lot No. 1TI75760, Exp. Date: Nov '97)

9. Dosing: On study days 1, 36, and 71, a single oral dose (1 x 50 mg) of test clomipramine HCl capsules or reference

clomipramine HCl capsules (ANAFRANIL) was administered to volunteers according to one of the following three regimens:

(1). 1 capsule of test product with 240 mL of room temperature water without breakfast.
(2). 1 capsule of test product with 240 mL of room temperature water after a standardized, high fat breakfast.
(3). 1 capsule of reference product with 240 mL of room temperature water after a standardized, high fat breakfast.

10. Food and fluid intake:

(1) Fluid Intake: No fluid except that given with the standardized breakfast (depending on randomization) and with drug administration was allowed from 1 hour before dosing until 2 hours after dose administration (see Schematic 2, Attachment 4). At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after the dose, water was allowed ad lib, if requested, but was generally controlled during confinement and limited to approximately 2400 mL from the time of dosing until release from the study site (see Schematic 2, Attachment 4).

(2) Fasting: All subjects fasted from 10 hours prior to dose administration or 9.5 hours prior to the standardized breakfast, as per randomization and fasted at least 4 hours after dosing. However, clear fluids, such as water, were allowed during fasting as described above in (1) Fluid Intake.

(3) Type of Meals: Subjects were served standardized meals and beverages. Meals were the same in content and quantity during each study period (for time schedule see Schematic 2, Attachment 4).

Breakfast: At 30 minutes before dosing, the appropriate randomized subjects were served a standardized high fat breakfast consisting of the following:

one buttered English Muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hash brown potatoes (4 oz.)
180 mL (6 fl. oz.) of orange juice
240 mL (8 fl. oz.) of whole milk

(4) Diet Restriction: No caffeine or xanthine-containing food or drink were allowed during the confinement portions of the study.

11. Confinement: From 10 hours before dosing until after the 24-hour blood draw in each period.

12. Washout period: 35 days.

13. Blood samples: Serial blood samples of 10 mL each were collected in Vacutainers with EDTA at the following times: predose (0), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 192, and 240 hours during each study period. The vacutainer samples were then transferred to the processing laboratory and centrifuged at 2400 RPM for 15 minutes at 4°C. The plasma was pipetted immediately with polyethylene pipettes into polypropylene screw-top transport tubes. The plasma samples were immediately placed in the freezer and stored at a temperature of -20°C or colder.

14. IRB and informed consent: The investigators provided the Institutional Review Board (IRB) with all appropriate material, including a copy of the protocol and consent document. The trial was not initiated until appropriate IRB written approval of the research plan and the consent document was obtained by the investigators and copies received by the Sponsor.

15. Pharmacokinetic and statistical analysis: SAS-GLM procedures were used on AUCT, AUCI, CMAX, TMAX, KE, THALF and blood levels at each sampling points. Test/Reference ratios were calculated for AUCT, AUCI, and CMAX.

IV. Assay Method Validation

A. Pre-study validation

1. Clomipramine

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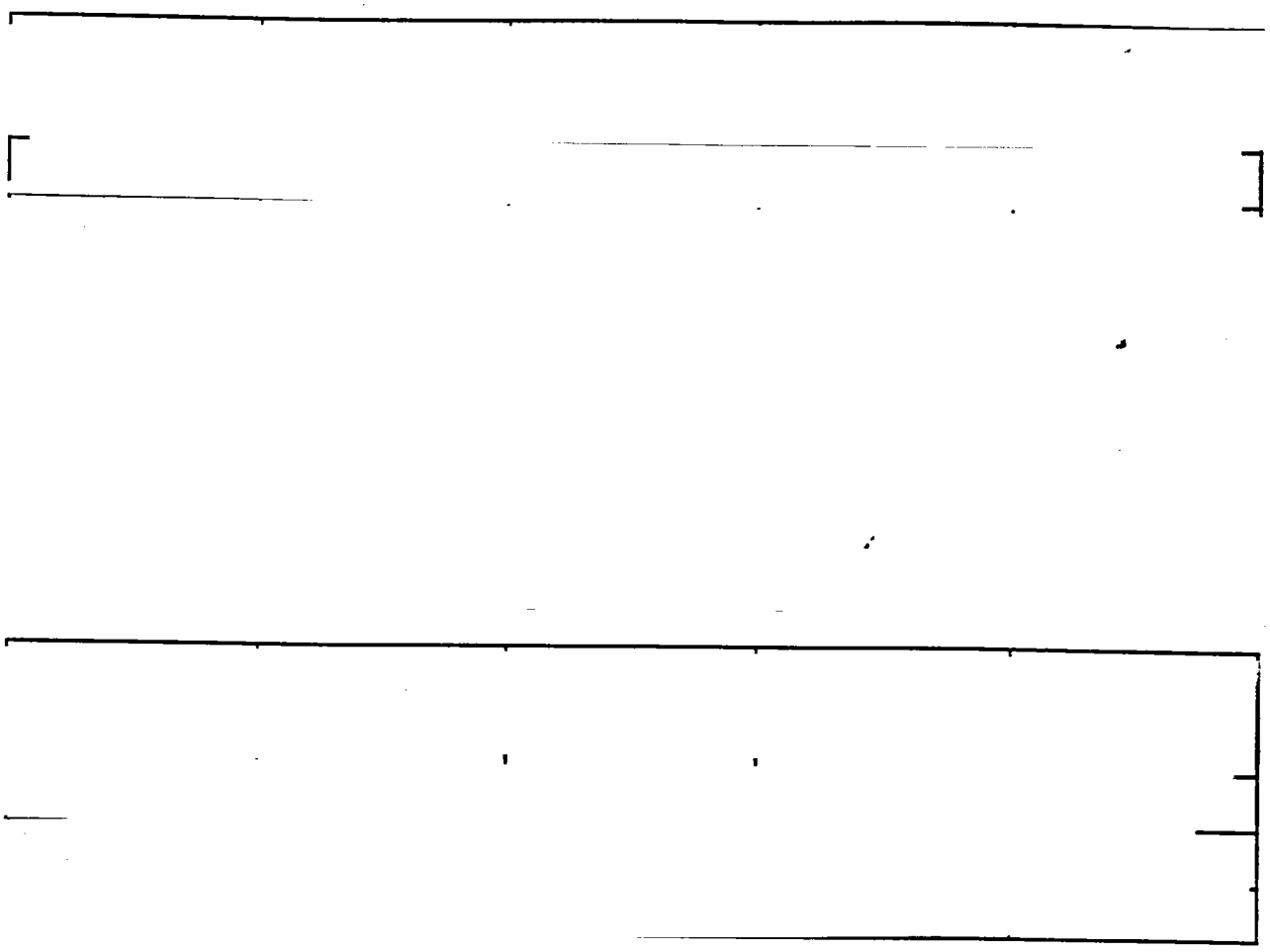
purged



V. In Vivo BE Studies Results with Statistical Analysis

A. Study under fasting conditions

Thirty-six (36) of thirty-eight (38) volunteers successfully completed the study. Subject 13 dropped prior to Period II dosing due to an illness. Subject 29 dropped prior to Period II dosing secondary to a schedule conflict. The assay results from Subjects 14 and 15 were rejected by the analytical laboratory, and no sample remained for reassay. Subject 26 vomited during the study and eliminated from the data analysis by this reviewer. Therefore only 33 subjects were used in the statistical analyses.

The subjects were monitored throughout the confinement portion of the study. Blood pressure and heart rate were obtained prior to

dosing and as scheduled following each dose. Dosing proceeded as authorized by the medical investigator who was available on-site and/or available by pager throughout the study.

Sixty-four adverse events were reported in twenty-one of 38 subjects dosed and included the following events (incidence): abdominal pain (1 - stomach ache), back pain (2 back ache), coughing (2; 1 - cough, 1 - coughing), diarrhea (3), dizziness (7; 1 - dizziness, 1 - feels dizzy, 5 - feels faint), dry heaves (3), dyspepsia (1 - upset stomach), earache, (right ear) (1), eczema (1 - eczema on both feet), fatigue (1 - tired), fever (1), headache (10; 9 - headache, 1 - sinus headache), hot flushes (2 - feels hot), hypertonia (1 - tight jaws), lymphadenopathy (1 - swollen glands), malaise (1 - body ache), nausea (5; 4 - nausea, 1 - slight nausea), paresthesia (1 - fingertips tingle) , pharyngitis (5 - sore throat) , respiratory disorder (3; 1 - nasal congestion, 1 - chest congestion, 1 - head congestion), rhinitis (7; 4 - runny nose ' , 3 - stuffy nose), rigors (2 - chills), sinusitis (1 - sinuses plugged), sweating increased (1 - sweats) , and vomiting (1)(subject #26). There were no serious adverse events or any events which required terminating any subject from the study.

1. Plasma levels of clomipramine and desmethylclomipramine

The plasma level-time profiles for clomipramine and desmethylclomipramine were similar for the test and reference products as shown in Table 9 (Fig. P-1) and Table 10 (fig. P-2), respectively.

Table 9. MEAN PLASMA CLOMIPRAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST MEAN; MEAN2=REF MEAN; RMEAN12=TEST/REF RATIO
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
N=33

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.74	1.74	1.51	1.48	1.15
1.5	7.97	4.69	6.20	3.88	1.29
2	12.14	6.06	10.53	6.11	1.15
3	17.65	7.26	15.60	6.60	1.13
4	20.12	7.28	18.60	7.04	1.08
5	20.42	7.43	21.47	8.24	0.95
6	19.09	6.54	19.20	7.14	0.99
8	14.56	5.74	15.00	6.37	0.97
10	11.14	4.48	11.42	5.52	0.97
12	8.62	3.64	8.88	4.30	0.97
24	4.89	2.19	5.11	2.91	0.96
48	2.28	1.56	2.37	1.69	0.97
72	1.09	1.22	1.07	1.29	1.02
96	0.60	0.93	0.49	0.86	1.22
120	0.20	0.61	0.21	0.68	0.94
144	0.12	0.50	0.08	0.47	1.46
192	0.05	0.29	0.04	0.25	1.15
240	0.03	0.17	0.00	0.00	.

Table 10. MEAN PLASMA DESMETHYLCLOMIPRAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST MEAN; MEAN2=REF MEAN; RMEAN12=TEST/REF RATIO
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
N=33

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.02	0.13	0.02	0.09	1.42
1.5	0.70	0.62	0.49	0.56	1.44
2	1.29	0.94	1.17	0.87	1.10
3	2.54	1.54	1.93	1.07	1.31
4	3.31	1.49	3.13	1.61	1.06
5	4.22	1.59	4.09	1.70	1.03
6	4.94	1.76	4.67	1.79	1.06
8	5.23	1.94	4.98	1.61	1.05
10	5.09	1.99	4.99	1.71	1.02
12	4.87	1.96	4.81	1.78	1.01
24	4.03	1.94	4.07	2.04	0.99
48	3.19	2.35	3.05	2.20	1.04
72	2.32	2.29	2.25	2.11	1.03
96	1.73	2.25	1.65	2.08	1.05
120	1.23	1.81	1.27	1.97	0.97
144	0.96	1.76	0.94	1.71	1.02
192	0.58	1.34	0.65	1.38	0.90
240	0.39	0.97	0.43	1.03	0.92

2. PK parameters of clomipramine and desmethylclomipramine

The Test/reference ratios for the log-transformed AUCT, AUCI and CMAX for clomipramine and desmethylclomipramine were all within 0.98-1.02 as shown in Tables 11-16. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX for clomipramine and desmethylclomipramine were all within 80-125% as shown in Tables 13 and 16, respectively.

There were sequence effect for LAUCT and period and sequence effects for LCMAX.

Table 11. ARITHMETIC MEANS AND RATIOS
for Clomipramine PK Parameters
MEAN1=TEST MEAN; MEAN2=REF MEAN; RMEAN12=TEST/REF RATIO
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
N=33

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	442.67	247.15	447.41	265.86	0.99
AUCT	392.21	227.34	388.55	245.20	1.01
CMAX	22.00	7.35	22.37	7.92	0.98
KE	0.03	0.01	0.03	0.02	0.94
LAUCI	388.78	0.51	392.92	0.50	0.99
LAUCT	340.28	0.54	334.61	0.55	1.02
LCMAX	20.83	0.34	21.03	0.37	0.99
THALF	27.75	16.49	25.63	13.64	1.08
TMAX	4.47	1.07	4.58	1.09	0.98

Table 12. LSMEANS AND RATIOS
for Clomipramine PK Parameters
LSM1=TEST LSMEAN; LSM2=REF LSMEAN; RLSM12=TEST/REF RATIO
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
N=33

PARAMETER	LSM1	LSM2	RLSM12
AUCI	447.19	447.01	1.00
AUCT	397.04	395.00	1.01
CMAX	22.18	22.72	0.98
LAUCI	392.71	392.02	1.00
LAUCT	344.53	340.33	1.01
LCMAX	21.02	21.39	0.98

Table 13. LSMEANS AND 90% CONFIDENCE INTERVALS
for Clomipramine PK Parameters
LSM1=TEST LSMEAN;LSM2=REF LSMEAN;LOWCI12=LOWER 90% CI;UPPCI12=UPPER 90% CI
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
N=33

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	447.19	447.01	94.40	105.68
AUCT	397.04	395.00	94.85	106.18
CMAX	22.18	22.72	92.70	102.57
LAUCI	392.71	392.02	94.29	106.43
LAUCT	344.53	340.33	94.99	107.88
LCMAX	21.02	21.39	92.85	104.05

Table 14. ARITHMETIC MEANS AND RATIOS
for Desmethylclomipramine PK Parameters
MEAN1=TEST MEAN; MEAN2=REF MEAN; RMEAN12=TEST/REF RATIO
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
N=33

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	509.10	560.33	509.84	574.92	1.00
AUCT	412.15	408.12	408.91	399.34	1.01
CMAX	5.59	2.05	5.48	1.79	1.02
KE	0.02	0.01	0.02	0.01	0.95
LAUCI	351.38	0.80	346.45	0.81	1.01
LAUCT	290.33	0.81	292.19	0.78	0.99
LCMAX	5.25	0.37	5.22	0.31	1.01
THALF	50.04	30.03	49.98	33.49	1.00
TMAX	11.58	11.86	13.27	14.65	0.87

Table 15. LSMEANS AND RATIOS
for Desmethylclomipramine PK Parameters
LSM1=TEST LSMEAN; LSM2=REF LSMEAN; RLSM12=TEST/REF RATIO
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
N=33

	LSM1	LSM2	RLSM12
PARAMETER			
AUCI	506.75	508.89	1.00
AUCT	411.58	410.12	1.00
CMAX	5.61	5.49	1.02
LAUCI	351.74	347.58	1.01
LAUCT	290.88	293.72	0.99
LCMAX	5.25	5.22	1.01

Table 16. LSMEANS AND 90% CONFIDENCE INTERVALS
for Desmethylclomipramine PK Parameters
LSM1=TEST LSMEAN;LSM2=REF LSMEAN;LOWCI12=LOWER 90% CI;UPPCI12=UPPER 90% CI
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
N=33

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCI	506.75	508.89	96.48	102.68
AUCT	411.58	410.12	96.06	104.65
CMAX	5.61	5.49	99.27	104.99
LAUCI	351.74	347.58	97.39	105.15
LAUCT	290.88	293.72	94.28	104.03
LCMAX	5.25	5.22	97.14	103.99

3. Test/Reference ratios for individual subjects

Test/Reference ratios for AUCT, AUCI, CMAX, TMAX, KE and THALF were summarized in Tables 17 and 19 for clomipramine and desmethylclomipramine, respectively. Statistics are shown in Tables 18 and 20.

Table 17. TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS
for Clomipramine
N=33

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	2						
3	3	2						
4	4	2						
5	5	1						
6	6	1						
7	7	1						
8	8	2						
9	9	2						
10	10	2						
11	11	1						
12	12	2						
13	16	2						
14	17	1						
15	18	2						
16	19	2						
17	20	2						
18	21	2						
19	22	2						
20	23	1						
21	24	1						
22	25	2						
23	27	1						
24	28	1						
25	30	2						
26	31	1						
27	32	1						
28	33	1						
29	34	1						
30	35	1						
31	36	2						
32	37	1						
33	38	2						

Table 18. STATISTICS ON THE TEST/REFERENCE RATIOS
for Clomipramine
N=33

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	33	1.04	0.24	0.68	1.85
RAUCI12	32	1.03	0.22	0.68	1.77
RCMAX12	33	1.01	0.23	0.66	1.66
RTMAX12	33	1.04	0.40	0.50	2.00
RKE12	32	0.96	0.24	0.42	1.52
RTHALF12	32	1.12	0.35	0.66	2.39

Table 19. TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS
for Desmethylclomipramine
N=33

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	2						
3	3	2						
4	4	2						
5	5	1						
6	6	1						
7	7	1						
8	8	2						
9	9	2						
10	10	2						
11	11	1						
12	12	2						
13	16	2						
14	17	1						
15	18	2						
16	19	2						
17	20	2						
18	21	2						
19	22	2						
20	23	1						
21	24	1						
22	25	2						
23	27	1						
24	28	1						
25	30	2						
26	31	1						
27	32	1						
28	33	1						
29	34	1						
30	35	1						
31	36	2						
32	37	1						
33	38	2						

Table 20. STATISTICS ON THE TEST/REFERENCE RATIOS
for Desmethylclomipramine
N=33

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	33	1.01	0.16	0.63	1.28
RAUCI12	33	1.02	0.13	0.73	1.36
RCMAX12	33	1.01	0.11	0.71	1.21
RTMAX12	33	0.99	0.35	0.17	2.00
RKE12	33	1.00	0.25	0.58	1.82
RTHALF12	33	1.07	0.27	0.55	1.72

4. AUCT/AUCI ratios for individual subjects

AUCT/AUCI ratios for individual subjects were shown in Tables 21 and 22 for clomipramine and desmethylclomipramine, respectively.

Table 21. AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS
for Clomipramine
N=33

OBS	SUB	TRT	AUCRATIO
1	1	1	
2	2	1	
3	3	1	
4	4	1	
5	5	1	
6	6	1	
7	7	1	
8	8	1	
9	9	1	
10	10	1	
11	11	1	
12	12	1	
13	16	1	
14	17	1	
15	18	1	
16	19	1	
17	20	1	
18	21	1	
19	22	1	
20	23	1	
21	24	1	
22	25	1	
23	27	1	
24	28	1	
25	30	1	
26	31	1	
27	32	1	
28	33	1	
29	34	1	
30	35	1	
31	36	1	
32	37	1	
33	38	1	
34	1	2	
35	2	2	
36	3	2	
37	4	2	
38	5	2	
39	6	2	
40	7	2	
41	8	2	
42	9	2	
43	10	2	
44	11	2	
45	12	2	
46	16	2	
47	17	2	
48	18	2	
49	19	2	
50	20	2	
51	21	2	
52	22	2	
53	23	2	

54	24	2
55	25	2
56	27	2
57	28	2
58	30	2
59	31	2
60	32	2
61	33	2
62	34	2
63	35	2
64	36	2
65	37	2
66	38	2

Table 22. AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS
for Desmethylclomipramine
N=33

OBS	SUB	TRT	AUCRATIO
1	1	1	
2	2	1	
3	3	1	
4	4	1	
5	5	1	
6	6	1	
7	7	1	
8	8	1	
9	9	1	
10	10	1	
11	11	1	
12	12	1	
13	16	1	
14	17	1	
15	18	1	
16	19	1	
17	20	1	
18	21	1	
19	22	1	
20	23	1	
21	24	1	
22	25	1	
23	27	1	
24	28	1	
25	30	1	
26	31	1	
27	32	1	
28	33	1	
29	34	1	
30	35	1	
31	36	1	
32	37	1	
33	38	1	
34	1	2	
35	2	2	
36	3	2	
37	4	2	
38	5	2	
39	6	2	
40	7	2	
41	8	2	
42	9	2	

43	10	2
44	11	2
45	12	2
46	16	2
47	17	2
48	18	2
49	19	2
50	20	2
51	21	2
52	22	2
53	23	2
54	24	2
55	25	2
56	27	2
57	28	2
58	30	2
59	31	2
60	32	2
61	33	2
62	34	2
63	35	2
64	36	2
65	37	2
66	38	2

B. Study under nonfasting conditions

Seventeen of eighteen volunteers successfully completed the study. Subject 14 failed to report for Period II check-in. The subjects were monitored throughout the confinement portion of the study. Blood pressure and heart rate were obtained prior to dosing and as scheduled following each dose. Dosing proceeded as authorized by the medical investigator who was available on-site and/or available by pager throughout the study. The 8 subjects who vomited (Subjects #2, 3, 10, 11, 13, 16, 17, and 18) were excluded from the statistical analysis by this reviewer. Only 9 subjects were used in the statistical analysis.

one hundred (100) adverse events were reported in sixteen (16) of eighteen (18) subjects dosed and included the following events (incidence) : asthenia (1 - weak) , chattering teeth (3), coughing (6; 4 - coughing, 2 -.cough), diarrhea (1), dizziness (3; 1 dizzy, 2 - lighthearted), dry heaves (1), dyspepsia (3; 1 - gas in stomach, 2 - upset stoma,@-,h), dysphonia (1 - hoarse voice),fatigue (4 - tired), headache (14), hot flushes (3 - hot), malaise (2 - achy) , mouth dry (2; 1 - dry mouth, 1 - dry throat) myalgia (2; 1 - right shoulder sprain, 1 - pulled neck muscles), nausea (13), pharyngitis (11 - sore throat), respiratory disorder (5; 3 - stuffy nose, 1 - stuffy head, 1 - congested head), rhinitis (6; 5 - runny nose, 1 - sneezing), somnolence (1 - groggy), sweating increased (1 - sweaty), syncope (1 - fainted), tremor (1 - very shaky) and vomiting (15) for 9 subjects (subjects #2, 3, 10, 11, 13, 14, 16, 17, and 18). There were no

serious adverse events or any events which required terminating any subject from the study.

In general, the clinical laboratory values were unremarkable over the course of the study.

1. Plasma levels of clomipramine and desmethylclomipramine

The plasma level-time profiles for clomipramine and desmethylclomipramine were similar for the test and reference products with or without food as shown in Table 23 (Fig. P-3) and Table 24 (fig. P-4), respectively. There was no discernable food effect for the parent drug and metabolite.

Table 23. MEAN PLASMA CLOMIPRAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FAST; MEAN2=TEST-FED; MEAN3=REF-FED; RMEAN23=MEAN2/MEAN3
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
N=9

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
1	3.77	3.32	8.14	12.15	4.13	5.64
1.5	9.09	5.79	13.87	14.12	11.30	13.84
2	14.98	8.52	21.63	19.04	18.42	15.82
3	22.60	11.39	22.15	14.61	24.12	14.61
4	24.82	13.14	24.13	13.84	26.83	11.01
5	25.69	10.61	25.39	7.82	29.64	11.52
6	23.19	8.82	23.94	4.86	28.49	10.47
8	19.09	8.88	19.77	4.03	23.03	8.61
10	13.40	6.16	14.70	1.78	17.67	5.83
12	11.02	5.73	12.14	2.61	13.21	5.70
24	7.13	4.94	7.30	2.40	8.11	3.22
48	3.73	2.80	3.67	1.97	4.06	2.50
72	2.02	1.91	2.16	1.38	2.29	1.58
96	1.38	1.60	1.29	1.14	1.31	1.23
120	0.70	1.49	0.72	0.98	0.62	1.06
144	0.50	1.07	0.31	0.92	0.40	0.84
192	0.23	0.68	0.15	0.46	0.17	0.51
240	0.15	0.46	0.12	0.36	0.11	0.33

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
1	0.46	0.91	1.97
1.5	0.66	0.80	1.23
2	0.69	0.81	1.17
3	1.02	0.94	0.92
4	1.03	0.93	0.90
5	1.01	0.87	0.86
6	0.97	0.81	0.84
8	0.97	0.83	0.86
10	0.91	0.76	0.83
12	0.91	0.83	0.92
24	0.98	0.88	0.90
48	1.02	0.92	0.90
72	0.93	0.88	0.94
96	1.07	1.05	0.98
120	0.97	1.12	1.15
144	1.64	1.26	0.77
192	1.47	1.35	0.91
240	1.29	1.39	1.08

Table 24. MEAN PLASMA DESMETHYLCLOMIPRAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FAST; MEAN2=TEST-FED; MEAN3=REF-FED; RMEAN23=MEAN2/MEAN3
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
N=9

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.12	0.35	0.00	0.00	0.09	0.26
1	0.28	0.45	0.54	0.74	0.27	0.42
1.5	1.05	0.97	1.22	1.27	0.86	0.81
2	1.71	1.04	2.42	2.31	1.63	1.29
3	2.99	1.32	2.76	1.84	2.81	1.64
4	3.96	1.62	3.65	2.29	3.69	2.05
5	5.19	1.92	5.08	2.14	4.72	1.76
6	5.77	2.39	5.38	1.76	5.12	1.97
8	6.05	2.96	5.80	2.03	5.48	2.25
10	6.11	3.48	5.55	1.79	5.53	2.33
12	5.79	2.79	5.57	2.36	5.62	2.94
24	5.08	3.21	5.01	2.56	4.87	2.39
48	4.42	3.61	4.23	3.29	4.47	3.68
72	3.51	3.44	3.45	3.24	3.70	3.82
96	2.92	3.35	2.80	3.33	2.93	3.31
120	2.52	3.42	2.35	2.93	2.60	3.41
144	2.03	3.23	1.98	3.11	2.08	3.37
192	1.53	2.73	1.40	2.43	1.70	2.99
240	1.23	2.39	1.22	2.35	1.19	2.25

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	1.31	0.00
1	0.52	1.05	2.00
1.5	0.86	1.22	1.42
2	0.71	1.05	1.49
3	1.08	1.06	0.98
4	1.09	1.07	0.99
5	1.02	1.10	1.07
6	1.07	1.13	1.05
8	1.04	1.10	1.06
10	1.10	1.11	1.00
12	1.04	1.03	0.99
24	1.01	1.04	1.03
48	1.04	0.99	0.95
72	1.02	0.95	0.93
96	1.04	1.00	0.96
120	1.07	0.97	0.91
144	1.03	0.98	0.95
192	1.09	0.90	0.83
240	1.01	1.04	1.03

2. PK parameters of clomipramine and desmethylclomipramine

The Test/reference ratios for the log-transformed AUCT, AUCI and CMAX for clomipramine and desmethylclomipramine under nonfasting conditions were all within 0.8-1.25 as shown in Tables 25-28.

Table 25. ARITHMETIC MEANS AND RATIOS
for Clomipramine PK Parameters
MEAN1=TEST-FAST; MEAN2=TEST-FED; MEAN3=REF-FED; RMEAN23=MEAN2/MEAN3
UNIT: CMAX=NG/ML AUC=NG HR/ML TIME=HRS
N=9

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	667.89	493.02	681.11	322.17	738.33	394.61
AUCT	600.89	459.10	613.56	298.89	673.56	374.17
CMAX	28.38	12.39	30.41	13.02	31.87	11.10
KE	0.02	0.01	0.02	0.01	0.02	0.01
LAUCI	555.82	0.60	628.51	0.41	665.60	0.46
LAUCT	491.78	0.63	563.89	0.42	601.84	0.48
LCMAX	26.20	0.42	28.31	0.39	30.28	0.33
THALF	34.37	18.08	37.56	20.40	34.91	18.32
TMAX	4.17	1.22	4.33	1.41	4.22	1.56

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	0.98	0.90	0.92
AUCT	0.98	0.89	0.91
CMAX	0.93	0.89	0.95
KE	0.99	0.98	1.00
LAUCI	0.88	0.84	0.94
LAUCT	0.87	0.82	0.94
LCMAX	0.93	0.87	0.93
THALF	0.91	0.98	1.08
TMAX	0.96	0.99	1.03

Table 26. LSMEANS AND RATIOS
for Clomipramine PK Parameters
LSM1=TEST-FAST; LSM2=TEST-FED; LSM3=REF-FED; RLSM23=LSM2/LSM3
UNIT: CMAX=NG/ML AUC=NG HR/ML TIME=HRS
N=9

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	803.70	780.20	822.67	1.03	0.98	0.95
AUCT	728.80	704.35	752.68	1.03	0.97	0.94
CMAX	31.84	31.78	33.49	1.00	0.95	0.95
LAUCI	650.67	704.47	734.88	0.92	0.89	0.96
LAUCT	580.76	632.35	666.47	0.92	0.87	0.95
LCMAX	29.51	29.82	31.88	0.99	0.93	0.94

Table 27. ARITHMETIC MEANS AND RATIOS
for Desmethylclomipramine PK Parameters
MEAN1=TEST-FAST; MEAN2=TEST-FED; MEAN3=REF-FED; RMEAN23=MEAN2/MEAN3
UNIT: CMAX=NG/ML AUC=NG HR/ML TIME=HRS
N=9

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	1093.00	1595.97	1062.78	1555.32	958.22	1226.53
AUCT	671.11	693.42	641.00	647.91	676.67	721.62
CMAX	6.93	3.43	6.39	2.49	6.64	3.29
KE	0.02	0.01	0.02	0.01	0.02	0.01
LAUCI	526.96	1.19	535.02	1.14	530.83	1.09
LAUCT	416.53	1.01	417.68	0.95	429.59	0.97
LCMAX	6.33	0.43	6.01	0.36	6.04	0.45
THALF	75.96	87.84	76.88	88.03	68.47	51.88
TMAX	25.78	37.64	13.00	13.34	18.22	16.95

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.03	1.14	1.11
AUCT	1.05	0.99	0.95
CMAX	1.09	1.04	0.96
KE	0.95	1.03	1.09
LAUCI	0.98	0.99	1.01
LAUCT	1.00	0.97	0.97
LCMAX	1.05	1.05	1.00
THALF	0.99	1.11	1.12
TMAX	1.98	1.41	0.71

Table 28. LSMEANS AND RATIOS
for Desmethylclomipramine PK Parameters
LSM1=TEST-FAST; LSM2=TEST-FED; LSM3=REF-FED; RLSM23=LSM2/LSM3
UNIT: CMAX=NG/ML AUC=NG HR/ML TIME=HRS
N=9

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1641.40	1533.36	1413.50	1.07	1.16	1.08
AUCT	920.75	894.15	936.56	1.03	0.98	0.95
CMAX	8.02	7.51	7.90	1.07	1.01	0.95
LAUCI	806.72	796.87	789.47	1.01	1.02	1.01
LAUCT	592.53	591.52	611.43	1.00	0.97	0.97
LCMAX	7.31	6.97	7.07	1.05	1.03	0.99

VI. *In Vitro* Testing and Waiver Requests

1. Formulation comparison

The test formulations for the three different strengths are shown in Table 29. The three formulations are proportional in active and inactive ingredients. The reference product contains starch, silicon dioxide, magnesium stearate, and other inactive ingredients for capsule shells.

Table 29. Test Formulations
Unit: mg

Ingredient	25 mg	50 mg	75 mg
Clomipramine Hydrochloride	25	50	75
Pregelatinized Starch			
Colloidal Silicon Dioxide			
Magnesium Stearate			
Total weight	162	324	486

2. Assay and content uniformity

Table 30 shows assay and content uniformity for the test and reference products. Expiry dates are listed for the reference products.

Table 30. Assay and Content Uniformity

Product	Assay, %	Content uniformity, % (%CV)
Test 50 mg, #K-19533, batch size capsules	103.1	98.3 (3.3)
Reference 50 mg, #1T175760, Exp:11/97	97.9	97.2 (2.5)
Test 25 mg, #K-19532	101.0	98.4 (4.1)
Reference 25 mg, #1T175496, Exp:9/97	103.5	101.2 (4.2)
Test 75 mg, #K-19534	97.7	99.6 (2.7)
Reference 75 mg, #1T167163, Exp:2/97	97.9	98.3 (2.2)

3. Dissolution testing

Pharmacopeial Forum method (March-April, '95) should be used for the dissolution testing of Clomipramine Hydrochloride Capsules. Currently this method is adopted as the FDA method. Instead, Lemmon used its own dissolution method. Only difference between the FDA and Lemmon's methods is that Lemmon uses 900 mL of 0.1 N HCL. The FDA method is shown below:

Medium and Volume	0.1 N HCL; 500 mL
Apparatus and rpm	Paddle; 50 rpm
Tolerances	(Q) in 30 min
Assay Method	

4. Waiver requests

The firm requested waivers for 25 mg and 75 mg strengths capsules. The waivers will not be granted until the firm submits acceptable dissolution data based on the FDA method.

VII. Comments

1. Study under fasting conditions: Thirty-three subjects were used in the statistical analyses for the fasting study. Thirty-eight subjects participated in the study, two dropped out, two showed assay problems, and one vomited during the study.

The plasma-time profiles for the test and reference products were comparable for the parent drug (clomipramine) and its active metabolite (desmethylclomipramine). The Test/Reference ratios for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, for clomipramine and desmethylclomipramine were within 0.8-1.25 range and their 90% confidence intervals were all within 80-125%.

2. Study under nonfasting conditions: Only 9 of 17 subjects who participated in the study, were used in the statistical analyses. Eight subjects vomited during the study and were eliminated from the statistical analyses.

   There was no discernable food effect for the test product. The plasma level-time profiles for the test product under fasting, test product under nonfasting, and reference product under nonfasting were comparable for the parent drug (clomipramine) and its active metabolite (desmethylclomipramine). The Test/reference ratios for the log-transformed AUCT, AUCI and CMAX for clomipramine and desmethylclomipramine under nonfasting conditions were all within 0.8-1.25.

3. Assay method validation: Assay validation data for the pre-study and within-study validations are acceptable.

4. Assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product (50 mg bio-batch #K19533) was capsules.

5. Comparative dissolution testing data based on the FDA method should be submitted. The firm submitted dissolution data based on its own method.

6. Formulations for the test products, 25 mg, 50 mg and 75 mg strengths capsules, are proportional in active and inactive ingredients.

7. Waivers for the 25 mg and 75 mg capsules will not be granted until acceptable dissolution data are submitted.

VIII. Deficiencies

Lemmon submitted the comparative dissolution testing data based on its own dissolution method. Pharmacopeial Forum method (March-April, '95) should be used for the dissolution testing of Clomipramine Hydrochloride Capsules. Currently this method is adopted as the FDA method.

IX. Recommendation

1. The *in vivo* bioequivalence studies conducted under fasting and nonfasting conditions by Lemmon on its Clomipramine Capsules, 50 mg strength, lot #K19533, comparing it to Basel's Anafranil^{R} Capsules, 50 mg strength, lot #1T175760, have been found incomplete. The firm should submit acceptable comparative dissolution testing data.

2. The following FDA dissolution testing should be conducted. The dissolution testing should be conducted in 500 mL of 0.1 N HCL at 37°C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of clomipramine hydrochloride in the dosage form is dissolved in 30 minutes.

The firm should be informed of the deficiency and recommendations.

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Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
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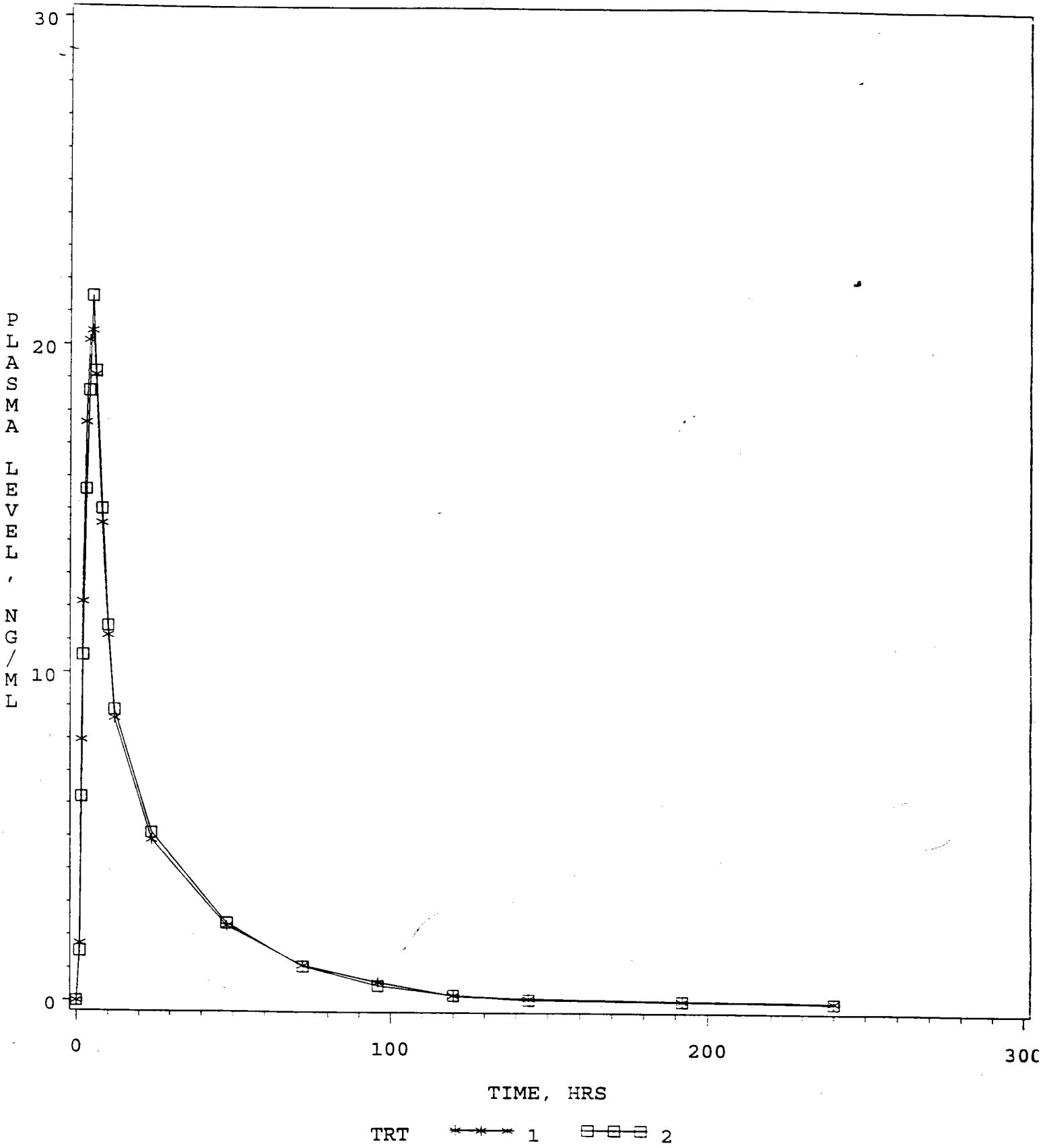
Team Leader, Review Branch III
Division of Bioequivalence

FIG P-1. PLASMA CLOMIPRAMINE LEVELS

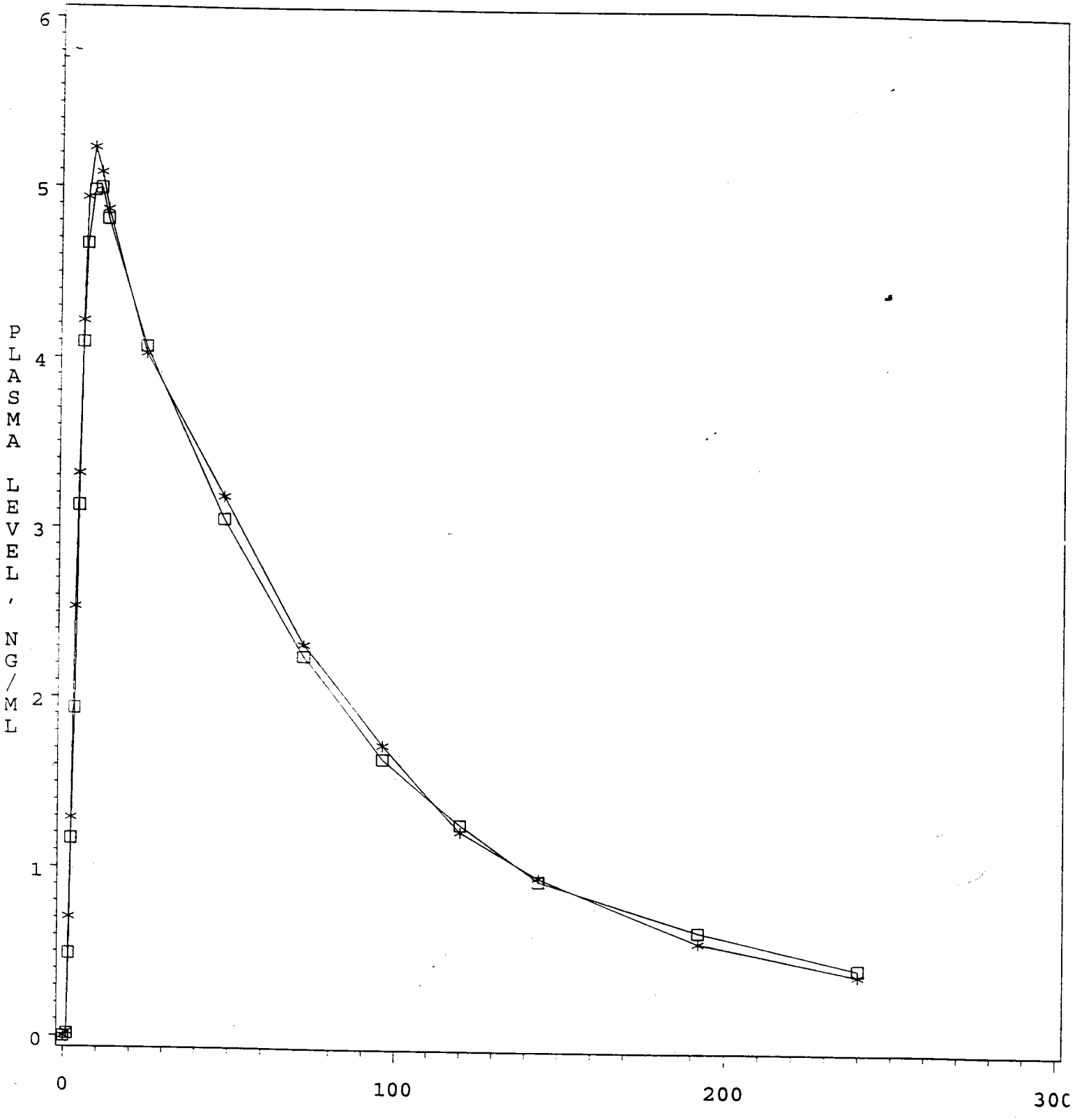
CLOMIPRAMINE TABLETS, 50 MG, ANDA #74-958
UNDER FASTING CONDITIONS
DOSE=50 MG



1=TEST PRODUCT(LEMMON) 2=REFERENCE PRODUCT(BASEL)

FIG P-2. PLASMA DESMETHYLCLOMIPRAMINE LEVELS

CLOMIPRAMINE TABLETS, 50 MG, ANDA #74-958
UNDER FASTING CONDITIONS
DOSE=50 MG



1=TEST PRODUCT(LEMMON) 2=REFERENCE PRODUCT(BASEL)

FIG P-3. PLASMA CLOMIPRAMINE LEVELS

CLOMIPRAMINE TABLETS, 50 MG, ANDA #74-958
UNDER NONFASTING CONDITIONS
DOSE=50 MG

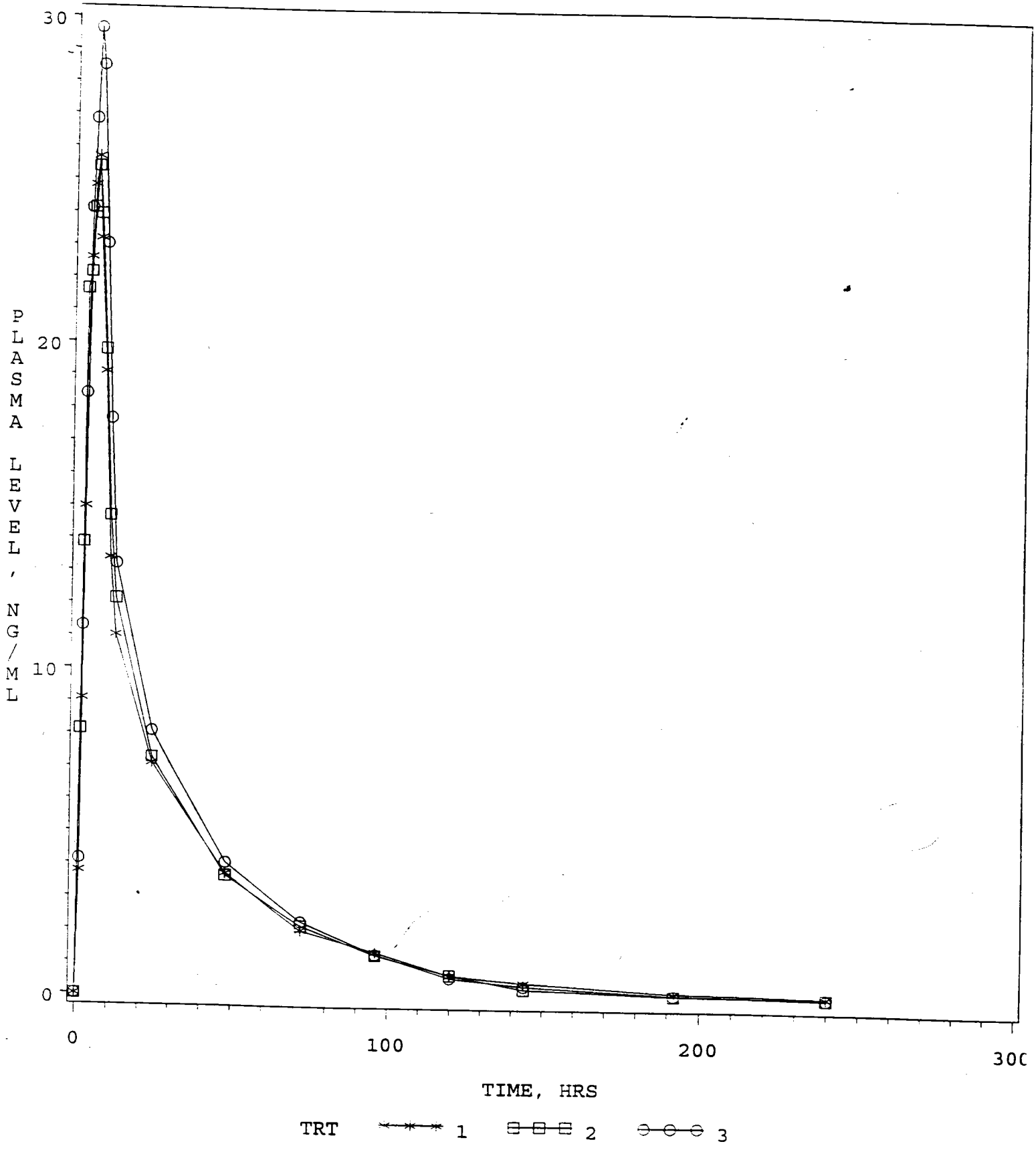


FIG P-4. PLASMA DESMETHYLCLOMIPRAMINE LEVELS

CLOMIPRAMINE TABLETS, 50 MG, ANDA #74-958
UNDER NONFASTING CONDITIONS
DOSE=50 MG